

# Thyroid Hormone Replacement Therapy in Primary Hypothyroidism: A Randomized Trial Comparing L-Thyroxine plus Liothyronine with L-Thyroxine Alone

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**Background:** Substituting part of the dose of L-thyroxine with small but supraphysiologic doses of liothyronine in hypothyroid patients has yielded conflicting results.

**Objective:** To evaluate combinations of L-thyroxine plus liothyronine in hypothyroid patients that match the proportions present in normal secretions of the human thyroid gland.

**Design:** Randomized, double-blind, crossover trial.

**Setting:** Academic research hospital.

**Participants:** 28 women with overt primary hypothyroidism.

**Intervention:** Crossover trial comparing treatment with L-thyroxine, 100 µg/d (standard treatment), versus treatment with L-thyroxine, 75 µg/d, plus liothyronine, 5 µg/d (combination treatment), for 8-week periods. All patients also received L-thyroxine, 87.5 µg/d, plus liothyronine, 7.5 µg/d (add-on combination treatment), for a final 8-week add-on period.

**Measurements:** Primary outcomes included serum thyroid hormone levels, results of quality-of-life and psychometric tests, and patients' preference. Multiple biological thyroid hormone end points were studied as secondary outcomes.

**Results:** Compared with standard treatment, combination treatment led to lower free thyroxine levels (decrease, 3.9 pmol/L [95% CI, 2.5 to 5.3 pmol/L]), slightly higher serum levels of

thyroid-stimulating hormone (increase, 0.62 mU/L [CI, 0.01 to 1.23 mU/L]), and unchanged free triiodothyronine levels. No improvement was observed in the other primary and secondary end points after combination treatment, with the exception of the Digit Span Test, in which the mean backward score and the mean total score increased slightly (0.6 digit [CI, 0.1 to 1.0 digit] and 0.8 digit [CI, 0.2 to 1.4 digits], respectively). The add-on combination treatment resulted in overreplacement. Levels of thyroid-stimulating hormone decreased by 0.85 mU/L (CI, 0.27 to 1.43 mU/L) and serum free triiodothyronine levels increased by 0.8 pmol/L (CI, 0.1 to 1.5 pmol/L) compared with standard treatment; 10 patients had levels of thyroid-stimulating hormone that were below the normal range. Twelve patients preferred combination treatment, 6 patients preferred the add-on combination treatment, 2 patients preferred standard treatment, and 6 patients had no preference ( $P = 0.015$ ).

**Limitations:** Treatment with L-thyroxine, 87.5 µg/d, plus liothyronine, 7.5 µg/d, was an add-on regimen and was not randomized.

**Conclusions:** Physiologic combinations of L-thyroxine plus liothyronine do not offer any objective advantage over L-thyroxine alone, yet patients prefer combination treatment.

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The recommended treatment for hypothyroidism is oral L-thyroxine sodium. This treatment is administered with the aim of restoring clinical euthyroidism and well-being and maintaining normal serum levels of thyroid-stimulating hormone (TSH) (1). However, triiodothyronine is the most active thyroid hormone because its affinity for the nuclear thyroid hormone receptor is 10- to 20-fold that of thyroxine (2, 3). The current practice of using L-thyroxine alone as replacement therapy for hypothyroidism assumes that peripheral conversion of thyroxine into triiodothyronine is able to restore normal triiodothyronine concentrations in target tissues. However, no experimental data support this assumption. On the contrary, we found that infusion of thyroxine alone into thyroidectomized rats was not able to restore euthyroidism (4); this was possible only by infusing combinations of thyroxine and triiodothyronine in proportions similar to those secreted by the rat thyroid gland (5).

An early study in hypothyroid patients compared treatment with the usual daily L-thyroxine dose, consisting of two or three 100-µg tablets, versus the same number of tablets, each containing 80 µg of L-thyroxine and 20 µg of

liothyronine (6). Although patients were probably overtreated throughout the study, adverse events were more frequent during treatment with the L-thyroxine–liothyronine combination (6), probably because of the excessive amount of liothyronine administered. More recently, several studies have evaluated combined levothyroxine–liothyronine treatment using a “triiodothyronine substitution” approach, in which a small yet supraphysiologic amount of liothyronine, ranging from 10 µg/d to 15 µg/d, was substituted for 50 µg of the total L-thyroxine dose (7–10). Bunevicius and colleagues (7, 8) reported that triiodothy-

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ronine substitution resulted in marked improvements in several items of the Profile of Mood States (POMS) and in a few indexes of psychometric function and quality of life, especially in athyreotic patients with thyroid cancer (8).

Recent studies, however, have failed to confirm any beneficial effects of triiodothyronine substitution on quality of life (9, 10). Even in selected hypothyroid patients presenting with depressive symptoms despite normalization of serum TSH concentrations, substitution of 50% of the L-thyroxine dose with a variable amount of liothyronine did not improve self-rated mood or well-being (11). However, 2 of these studies had a parallel-group design (10, 11), and in the study that included a crossover design, serum TSH levels were higher after triiodothyronine substitution than after treatment with L-thyroxine alone (9), suggesting undertreatment with the former agent (12).

These recent studies using triiodothyronine substitution had limitations. The ratios of L-thyroxine to liothyronine in the individual combinations administered to patients varied widely and differed from the physiologic ratio of thyroxine to triiodothyronine and from the absolute quantities of both hormones secreted by the human thyroid gland (5, 13). Moreover, these studies included men and women whose hypothyroidism varied in duration and severity. Some had subclinical hypothyroidism and might have retained some residual secretion of thyroxine and triiodothyronine. Prestudy L-thyroxine requirements also differed among patients. Therefore, the lack of beneficial effects of the combinations over L-thyroxine alone might depend not on the treatment itself but on these confounding factors. To avoid the limitations of previous studies, we examined L-thyroxine–liothyronine combinations with fixed ratios based on human thyroid secretion (14) in women with overt hypothyroidism at diagnosis.

## METHODS

### Study Objective and Participants

We performed this study to evaluate whether combinations of L-thyroxine plus liothyronine matching the proportion present in the normal secretion of the human thyroid gland offer demonstrable advantages over standard treatment with L-thyroxine alone in patients with overt primary hypothyroidism. We included women who were between 18 and 70 years of age; who presented with overt primary hypothyroidism, as defined by increased TSH levels and decreased serum free thyroxine levels at diagnosis; and who had maintained normal serum TSH levels while receiving treatment with a stable L-thyroxine dosage of 100  $\mu\text{g}/\text{d}$  for at least the previous year. Exclusion criteria were mental illness; affective disorders or use of psychotropic drugs; cardiovascular, renal, or hepatic disease; or osteoporosis. For the external euthyroid control group, we selected healthy women who were similar to the patients in terms of age, postmenopausal status, ethnicity, social and cultural background, academic degrees, and current professional

### Context

Studies comparing the outcomes of treatment of hypothyroidism with L-thyroxine alone versus with a combination of L-thyroxine and liothyronine have had conflicting results. Some experts believe the conflicting results occurred because some studies used supraphysiologic doses of liothyronine.

### Contribution

This crossover trial compared L-thyroxine with a combination of physiologic doses of L-thyroxine and liothyronine and found no objective advantages of combination therapy.

### Implications

Treatment of hypothyroidism with L-thyroxine alone is sufficient.

—The Editors

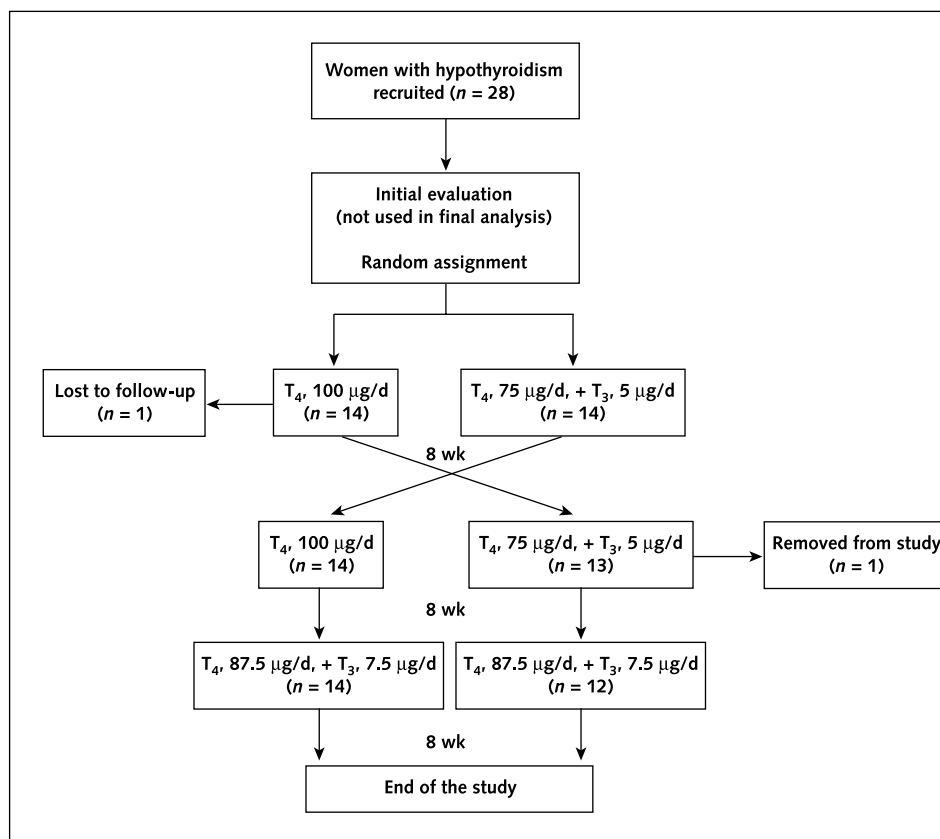
occupation. Patients and controls were not taking any drug known to influence thyroid function, other than L-thyroxine in the former group. The Ethics Committee of the Hospital Ramón y Cajal approved the study, and written informed consent was obtained from all patients and controls.

### Interventions

We used a randomized, double-blind, crossover design to compare treatment with L-thyroxine, 100  $\mu\text{g}/\text{d}$  (standard treatment), and treatment with a combination of L-thyroxine, 75  $\mu\text{g}/\text{d}$ , plus liothyronine, 5  $\mu\text{g}/\text{d}$  (combination treatment), in periods of 8 weeks each (Figure 1). The latter combination was selected after we considered the 14-to-1 proportion of thyroxine to triiodothyronine in human thyroid secretion (14) and the intestinal absorption of both hormones. Because our previous experience in rats indicated that it is difficult to guess the correct L-thyroxine–liothyronine combination, and because we feared that the combination we chose might result in undertreatment, all patients were also given a daily combination containing 87.5  $\mu\text{g}$  of L-thyroxine plus 7.5  $\mu\text{g}$  of liothyronine (add-on combination treatment) for a final 8-week add-on period (Figure 1).

On a daily basis, patients took one 50- $\mu\text{g}$  tablet of L-thyroxine (Euthyrox, Merck KgaA, Darmstadt, Germany) from a red-tagged opaque box and another tablet from a yellow-tagged opaque box. The content of the yellow-tagged box differed during every 8-week period and contained 50- $\mu\text{g}$  L-thyroxine tablets (Levothyroid, Aventis, Madrid, Spain) for standard treatment; Novothyral Mite tablets (Merck), containing 25  $\mu\text{g}$  of L-thyroxine plus 5  $\mu\text{g}$  of liothyronine, for combination treatment; or half-tablets of Novothyral 75 (Merck), containing 37.5  $\mu\text{g}$  of L-thyroxine plus 7.5  $\mu\text{g}$  of liothyronine, for the add-on combination treatment.

Figure 1. Flow of patients through the study.



T<sub>3</sub> = liothyronine (synthetic triiodothyronine); T<sub>4</sub> = L-thyroxine (synthetic thyroxine).

## Outcomes

Primary outcomes included serum thyroid hormone levels, POMS, the Digit Symbol Substitution Test, the Digit Span Test, the Visual Scanning Test, and patients' preference. Other tests of quality of life and psychometric function and multiple biological thyroid hormone end points were studied as secondary outcomes. We performed the same procedures in patients at 4 different times: when they were receiving their usual L-thyroxine treatment before the start of the study and at the end of each treatment period. Patients were evaluated while receiving usual treatment to avoid a placebo effect related to the fact of being evaluated; these data were not included in the final analysis. Controls were evaluated only once.

Patients and controls reported to the hospital after fasting overnight for 12 hours. Patients took the study medication with water immediately after waking up. Body mass index, office blood pressure, waist-to-hip ratio, body composition (estimated by bioelectrical impedance [BF-300, Omron Healthcare Inc., Bannockburn, Illinois]), and body temperature were measured. Immediately afterward, a broad evaluation of biological thyroid hormone end points was performed. The sequence of this evaluation was the same for every participant and lasted for no more than 3 hours.

## Cardiovascular Evaluation

A single investigator performed echocardiography in all participants as described previously (15). The following measurements were recorded: left atrial diameter, systolic and diastolic left ventricular diameter, posterior wall and septum thickness, shortening fraction, left ventricular ejection fraction, left ventricular mass index, early-phase and maximal late mitral valve flows and their ratio, isovolumic relaxation time, deceleration time, aortic velocity time integral, heart rate, and cardiac output. Systemic vascular resistance was calculated as the mean arterial blood pressure divided by cardiac output. Patients were asked to record their heart rate using an oscillometric ambulatory blood pressure monitor (A&D Company Ltd., Tokyo, Japan) for 24 hours to exclude liothyronine-induced tachycardia.

## Hormonal and Biochemical Measurements

Blood samples were obtained 2 hours after ingestion of study medication. Serum levels of free thyroxine, free triiodothyronine, TSH, and sex hormone-binding globulin were determined by using immunochemiluminescent assays (Immulite 2000, Diagnostic Products Corp., Los Angeles, California). The normal ranges were 0.4 to 4.0

mU/L for serum TSH, 10.3 to 24.5 pmol/L for free thyroxine, and 2.8 to 6.5 pmol/L for free triiodothyronine, as reported by the Central Laboratory of Hospital Ramón y Cajal.

An automated analyzer was used to perform a complete serum biochemistry analysis, including renal and liver function tests and lipid profiles, and to measure 24-hour urinary creatinine, calcium, and phosphate excretion (Aeroset, Abbott Laboratories, Abbot Park, Illinois). Levels of urinary hydroxyproline, pyridolines, and deoxypyridolines were determined by using chromatography (Bio-Rad Laboratories, Hercules, California). The mean coefficients of variation were below 10% for all of these assays.

### Central and Peripheral Nervous System Evaluation

Immediately after blood sampling, participants had a small breakfast and an independent evaluator performed a battery of cognitive, affective, and quality-of-life tests, including the Zulewski score (16), POMS (17), Nottingham Health Profile and Short Form-36 Health Survey (18–22), Digit Symbol Substitution Test (23, 24), Digit Span Test (23), Visual Scanning Test (25, 26), and 16 Visual Analogue Mental Scales (VAMS) (sadness, confusion, fear, depression, irritability, tension, anger, tiredness, agitation, feeling cold, blurred vision, nausea, sleep, lightheadedness, drowsiness, and feeling hot, as previously described in detail [27]). Central and peripheral nervous system performance was objectively estimated by measuring the ankle reflex relaxation time (Cardioline, Elettronica Trentina, Cavareno, Italy) and obtaining visual and brainstem auditory evoked potentials (28, 29). At the end of the study, patients were asked which treatment they preferred.

### Sample Size

We based our a priori power analysis on the beneficial effects of triiodothyronine substitution previously reported by Bunevicius and colleagues (7, 8). Calculations were done for a repeated-measures design, considering the autocorrelation of each test and setting  $\alpha$  at 0.05, using PASS2000 software (Number Cruncher Statistical Systems, Kaysville, Utah). Our sample size provided 80% power to detect differences between the mean values after treatment of 2.1 points in the fatigue–inertia score, 3.6 points in the depression–dejection score, and 2.7 points in the anger–hostility score of the POMS; 0.5 digit in the total score of the Digit Span Test; and 1 point in the “items found” score of the Visual Scanning Test.

### Randomization, Implementation, and Blinding

One investigator, who had no contact with the patients throughout the study, designed the protocol, obtained the computer-generated sequence of randomization, assigned participants to their groups, and prepared the boxes with the tablets. The physicians recruiting the patients, administering the interventions, and evaluating the outcomes were blinded to the design of the study and to the medication contained in the boxes. Blinding was main-

tained throughout the study. The study pills were counted to assess adherence only after all of the patients had completed the study. Adherence was 98%, 99%, and 98% for standard treatment, combination treatment, and add-on combination treatment, respectively.

### Statistical Analysis

Data are presented as means with 95% CIs, unless otherwise stated. Logarithm or square root transformations were applied to ensure normality whenever possible. For normally distributed outcomes, the comparisons of standard treatment and combination treatment were evaluated with corrected *t*-tests by using the crossover analysis tools of NCSS 2004 software (Number Cruncher Statistical Systems). For outcomes that were not normally distributed after transformations, we compared treatments with Hodges–Lehman estimates of point median differences and exact 95% CIs, using StatXact software (Cytel Software Corp., Cambridge, Massachusetts) (30, 31).

The add-on combination treatment was compared with standard treatment by using paired *t*-tests or Wilcoxon signed-rank tests, as appropriate. Comparisons of the different treatments used in hypothyroid patients with controls were performed by using 1-way analysis of variance followed by the Dunnett test or by Kruskal–Wallis analysis of variance followed by Mann–Whitney tests, as appropriate. Discontinuous variables were analyzed by using the chi-square test. These analyses were performed by using SPSS for Macintosh, version 10 (SPSS, Inc., Chicago, Illinois). *P* values less than 0.05 were considered statistically significant.

### Role of the Funding Sources

The funding sources (Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo and Consejería de Educación, Comunidad de Madrid, Spain, and Merck KgaA, Darmstadt, Germany) had no role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

## RESULTS

Twenty-eight hypothyroid patients (mean age [ $\pm$ SD],  $48 \pm 11$  years; mean body mass index [ $\pm$ SD],  $25.9 \pm 7.1$  kg/m<sup>2</sup>) were recruited from October 2000 to January 2003. Twenty healthy women (mean age [ $\pm$ SD],  $46 \pm 13$  years; mean body mass index [ $\pm$ SD],  $25.4 \pm 5.7$  kg/m<sup>2</sup>) served as the external euthyroid control group. Causes of overt hypothyroidism were chronic lymphocytic thyroiditis in 23 patients and thyroid ablation for Graves disease or toxic multinodular goiter in 5 patients.

Two patients did not complete the study (Figure 1). One was lost to follow-up while receiving standard treatment. The other was removed from the study because of asymptomatic thyrotoxicosis after combination treatment, related to the ingestion of a homeopathic preparation con-

taining desiccated thyroid extract. Her thyroid hormone levels returned to normal after the homeopathic compound was withdrawn, but her data were not used for analysis. The results from the 26 patients who completed the 3 treatment regimens are included in the final analysis.

#### Crossover Study Comparing Standard Treatment (L-Thyroxine, 100 µg/d) with Combination Treatment (L-Thyroxine, 75 µg/d, plus Liothyronine, 5 µg/d)

The results of the primary outcomes are presented in **Figure 2** and **Table 1**. Compared with standard treatment, serum levels of free thyroxine decreased by 3.9 pmol/L (95% CI, 2.5 to 5.3 pmol/L) after combination treatment, whereas serum TSH levels increased slightly by 0.62 mU/L (CI, 0.01 to 1.23 mU/L) and levels of free triiodothyronine remained unchanged (**Table 1**). No improvement after combination treatment was observed in any scale of the POMS, on the Digit Symbol Substitution Test, or on the Visual Scanning Test. However, combination treatment slightly improved the backward and total scores of the Digit Span Test (0.6 digit [CI, 0.1 to 1.0 digit] and 0.8 digit [CI, 0.2 to 1.4 digit], respectively) (**Table 1**). At the end of the study, 12 patients preferred combination treatment, 6 preferred the add-on combination treatment, 2 preferred standard treatment, and 6 had no preference (chi-square value, 10.46;  $P = 0.015$ ).

The results of the most important secondary outcomes are presented in **Table 1**. The remainder can be found in the **Appendix Table** (available at [www.annals.org](http://www.annals.org)). As occurred with other tests of quality of life and psychometric function, no statistically significant differences between standard and combination treatment were observed in any scale of the Nottingham Health Profile or the Short Form-36 Health Survey or in any VAMS.

Compared with standard treatment, combination treatment led to an increase of 0.1 °C (CI, 0.1 to 0.2 °C) in body temperature, an increase of 0.4 mmol/L (16 mg/dL) (CI, 0.2 to 0.7 mmol/L [8 to 27 mg/dL]) in total cholesterol level, an increase of 0.4 mmol/L (16 mg/dL) (CI, 0.1 to 0.6 mmol/L [4 to 23 mg/dL]) in low-density lipoprotein cholesterol level, and an increase of 1.6 µmol (CI, 0.1 to 3.4 µmol) in the ratio of urinary deoxypyridolines to creatinine (**Table 1**). Cardiac output showed a small decrease of 0.2 L/min (CI, 0.01 to 0.4 L/min), related to a subtle decrease in heart rate of 3.0 beats/min (CI, 0.4 to 5.7 beats/min) (**Appendix Table**, available at [www.annals.org](http://www.annals.org)). No statistically significant differences between standard and combination treatment were observed in other secondary outcomes, including clinical, biochemical, and hormone measurements; ankle reflex relaxation time; evoked potentials; or echocardiographic measurements (**Appendix Table**, available at [www.annals.org](http://www.annals.org)).

#### Add-On Combination Treatment (L-Thyroxine, 87.5 µg/d, plus Liothyronine, 7.5 µg/d)

Regarding primary outcomes, the add-on combination treatment resulted in overreplacement. Levels of TSH de-

creased by 0.85 mU/L (CI, 0.27 to 1.43 mU/L), and levels of free triiodothyronine increased by 0.8 pmol/L (CI, 0.1 to 1.5 pmol/L) compared with standard treatment (**Table 2**). In 10 women, TSH levels were below the lower limit of the normal range but were not suppressed. No statistically significant differences were observed for the add-on combination treatment compared with standard treatment in any scale of the POMS or the Digit Span Test. On the contrary, when compared with standard treatment, patients receiving the add-on combination treatment performed better on the copies score of the Digit Symbol Substitution Test (increase, 8.5 points [CI, 3.0 to 14.0 points]) and on the time needed to complete the Visual Scanning Test (decrease, 10.0 seconds [CI, 0.9 to 26.0 seconds]) (**Table 2**).

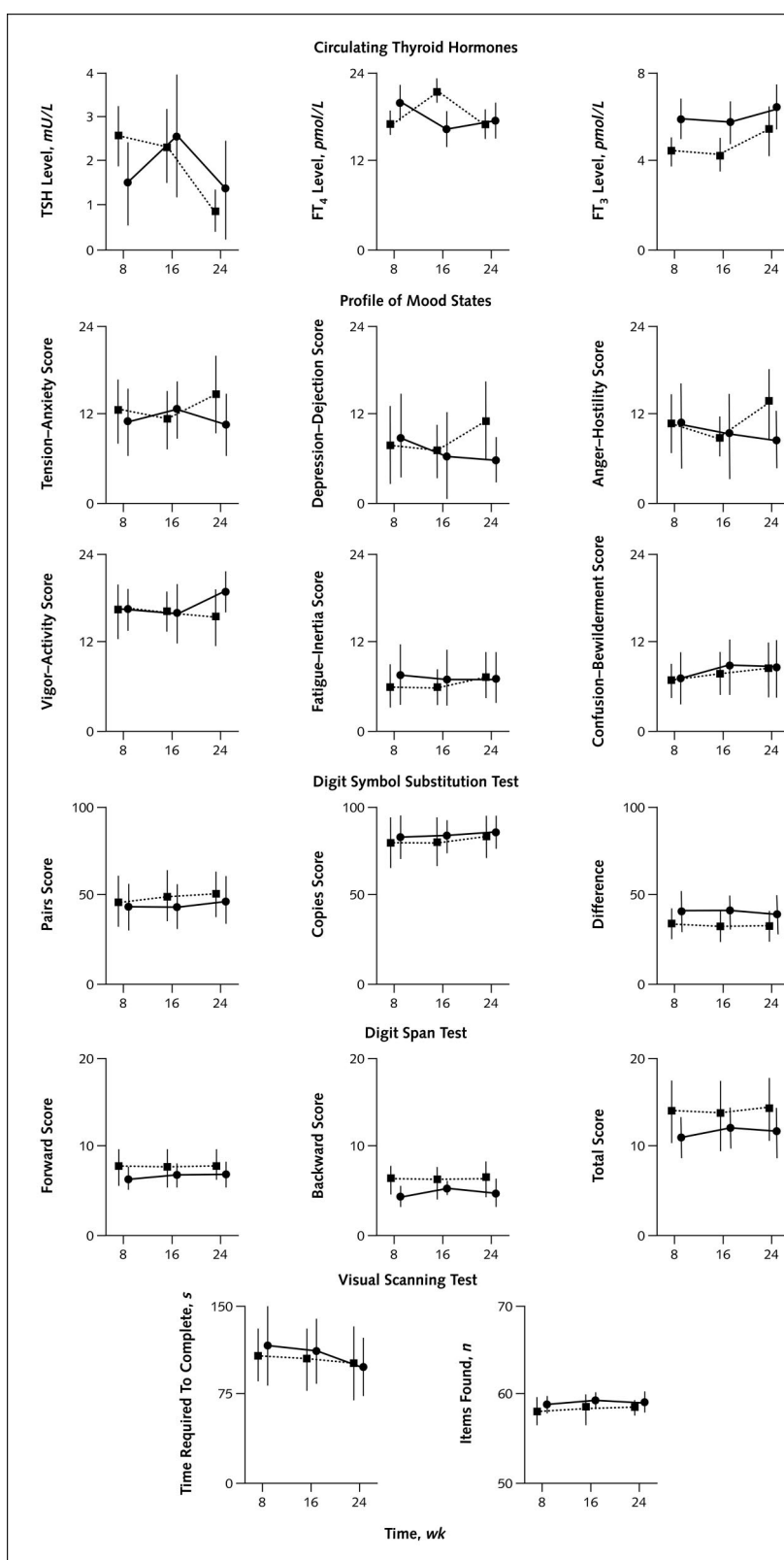
With respect to secondary outcomes, no statistically significant differences were observed in any scale of the Nottingham Health Profile and the Short Form-36 Health Survey or in any VAMS compared with standard treatment (**Appendix Table**, available at [www.annals.org](http://www.annals.org)). Moreover, the number of patients who scored abnormal values on any category of the quality-of-life tests according to population standards did not differ depending on the treatment applied.

Compared with standard treatment, body temperature in patients receiving the add-on combination treatment increased by 0.2 °C (CI, 0.1 to 0.3 °C), and the Zulewski score decreased by 1.0 point (CI, 0.1 to 1.5 points) (**Table 2**). Serum creatinine concentration decreased by 3.2 µmol/L (0.04 mg/dL) (CI, 0.4 to 5.9 µmol/L [0.01 to 0.07 mg/dL]), whereas urinary bone-remodeling markers increased after the add-on combination treatment compared with standard treatment. The hydroxyproline-creatinine ratio increased by 0.5 mmol (CI, 0.09 to 1.23 mmol), the pyridoxines-creatinine ratio increased by 10.1 µmol (CI, 2.5 to 17.7 µmol), and the pyridolines-creatinine ratio increased by 2.8 µmol (CI, 1.5 to 4.0 µmol), suggesting that the add-on combination regimen led to overtreatment (**Table 2**, **Appendix Table** [available at [www.annals.org](http://www.annals.org)]). There were also statistically significant differences in the isovolumic relaxation time and the left III latency of brainstem auditory evoked potentials (**Appendix Table**, available at [www.annals.org](http://www.annals.org)). However, considering the large number of variables tested in our study, and considering that we did not correct for multiple testing, it is possible that some of these differences might have resulted from chance instead of being actually present in the sample. Finally, no statistically significant differences were found in other clinical or biochemical variables or in the ankle reflex relaxation time (**Table 2**, **Appendix Table** [available at [www.annals.org](http://www.annals.org)]).

#### Comparison with External Euthyroid Controls

The results of the primary outcomes and the most important secondary outcomes obtained from the control group are presented in **Table 3** and in the **Appendix Table** (available at [www.annals.org](http://www.annals.org)). Standard treatment resulted

Figure 2. Evolution of primary outcomes during the study depending on the sequence of treatment.



Data are means with 95% CIs. Squares indicate the following treatment sequence: 1) L-thyroxine, 75  $\mu\text{g}/\text{d}$ , plus liothyronine, 5  $\mu\text{g}/\text{d}$ ; 2) L-thyroxine, 100  $\mu\text{g}/\text{d}$ ; 3) L-thyroxine, 87.5  $\mu\text{g}/\text{d}$ , plus liothyronine, 7.5  $\mu\text{g}/\text{d}$  ( $n = 14$ ). Circles indicate the following treatment sequence: 1) L-thyroxine, 100  $\mu\text{g}/\text{d}$ ; 2) L-thyroxine, 75  $\mu\text{g}/\text{d}$ , plus liothyronine, 5  $\mu\text{g}/\text{d}$ ; 3) L-thyroxine, 87.5  $\mu\text{g}/\text{d}$ , plus liothyronine, 7.5  $\mu\text{g}/\text{d}$  ( $n = 12$ ). FT<sub>3</sub> = free triiodothyronine; FT<sub>4</sub> = free thyroxine; TSH = thyroid-stimulating hormone.

Table 1. Primary and Selected Secondary Outcomes in the 26 Hypothyroid Patients Who Completed the Crossover Study\*

Outcome	Standard Therapy†	Combination Therapy‡	Adjusted Difference (95% CI)§
<b>Biochemical variables</b>			
TSH level, <i>mU/L</i>	1.95 ± 1.44	2.56 ± 1.65	0.62 (0.01 to 1.23)
Free thyroxine level, <i>pmol/L</i>	20.7 ± 3.4	16.8 ± 3.1	-3.9 (-5.3 to -2.5)
Free triiodothyronine level, <i>pmol/L</i>	5.1 ± 1.5	5.0 ± 1.4	-0.03 (-0.7 to 0.6)
Combination therapy first ( <i>n</i> = 14)	4.3 ± 1.2	4.4 ± 1.0	
Standard therapy first ( <i>n</i> = 12)	5.9 ± 1.4	5.8 ± 1.4	
SHBG level, <i>nmol/L</i>	35.9 ± 24.0	31.5 ± 22.8	-4.4 (-9.7 to 1.0)
Total cholesterol level			
In <i>mmol/L</i>	5.2 ± 1.0	5.6 ± 1.1	0.4 (0.2 to 0.7)
In <i>mg/dL</i>	201 ± 39	217 ± 43	16 (8 to 27)
LDL cholesterol level			
In <i>mmol/L</i>	3.0 ± 1.0	3.4 ± 1.0	0.4 (0.1 to 0.6)
In <i>mg/dL</i>	116 ± 39	132 ± 39	16 (4 to 23)
Combination therapy first ( <i>n</i> = 14), <i>mmol/L (mg/dL)</i>	2.7 ± 1.0 (104 ± 39)	3.0 ± 1.0 (116 ± 39)	
Standard therapy first ( <i>n</i> = 12), <i>mmol/L (mg/dL)</i>	3.4 ± 0.9 (132 ± 35)	3.8 ± 0.9 (147 ± 35)	
Ratio of urinary deoxyipyridolines to creatinine, <i>μmol  </i>	9.4 ± 3.4	10.8 ± 4.4	1.6 (0.1 to 3.4)
<b>Clinical variables</b>			
Ankle reflex relaxation time, <i>ms</i>	0.18 ± 0.02	0.18 ± 0.02	0.00 (-0.02 to 0.02)¶
Zulewski score	0.5 ± 0.6	0.4 ± 0.9	0.0 (0.0 to 1.0)¶
Body temperature, °C	36.4 ± 0.2	36.6 ± 0.2	0.1 (0.1 to 0.2)
Combination therapy first ( <i>n</i> = 14)	36.5 ± 0.3	36.7 ± 0.2	
Standard therapy first ( <i>n</i> = 12)	36.3 ± 0.1	36.4 ± 0.2	
<b>Profile of Mood States scores</b>			
Tension-anxiety	11.1 ± 6.5	12.1 ± 6.8	1.2 (-1.3 to 3.8)
Depression-dejection	7.8 ± 7.4	7.1 ± 8.9	-0.8 (-3.4 to 1.8)
Anger-hostility	9.5 ± 7.3	9.9 ± 7.8	0.2 (-2.0 to 2.5)
Vigor-activity	16.3 ± 4.4	16.2 ± 6.3	-0.2 (-2.8 to 2.5)
Fatigue-inertia	6.7 ± 5.4	6.6 ± 5.3	-0.1 (-2.2 to 2.0)
Confusion-bewilderment	7.5 ± 4.9	7.7 ± 4.9	0.3 (-1.5 to 2.0)
<b>Cognitive performance scores</b>			
Digit Symbol Substitution Test			
Pairs	45.9 ± 21.4	44.7 ± 21.3	-1.1 (-4.0 to 1.9)
Copies	81.5 ± 20.5	81.2 ± 19.9	0.0 (-18.0 to 14.5)¶
Difference	35.7 ± 15.8	36.5 ± 14.3	0.7 (-3.0 to 4.4)
Digit Span Test			
Forward	7.1 ± 3.0	7.3 ± 2.9	0.2 (-0.3 to 0.7)
Backward	5.3 ± 2.6	5.8 ± 2.2	0.6 (0.1 to 1.0)
Total	12.4 ± 5.3	13.2 ± 4.9	0.8 (0.2 to 1.4)
Visual Scanning Test			
Time	109.3 ± 46.6	109.0 ± 39.5	-0.5 (-11.9 to 10.8)
Items found	58.5 ± 2.1	58.6 ± 2.2	0.0 (-1.0 to 1.0)¶
Errors	0.0 ± 0.0	0.0 ± 0.0	0.0 (0.0 to 0.0)¶
<b>Quality-of-life scores</b>			
SF-36-general health	60.9 ± 17.1	62.2 ± 17.5	1.2 (-2.3 to 4.7)
NHP			
Total	8.8 ± 6.8	8.5 ± 6.4	-0.3 (-1.8 to 1.5)
Emotional	13.1 ± 10.8	14.4 ± 12.6	0.0 (-4.8 to 7.2)¶
Energy	3.8 ± 6.7	3.8 ± 5.8	0.0 (-7.0 to 7.0)¶
Social	4.8 ± 10.3	6.9 ± 14.3	6.9 (-13.9 to 27.8)¶
<b>Visual Analogue Mental Scale scores</b>			
Depressed	23.8 ± 28.8	23.9 ± 29.4	0.2 (-7.7 to 7.4)
Blurred vision	25.2 ± 29.1	27.1 ± 29.8	0.0 (-7.0 to 12.0)¶
Nauseated	12.5 ± 21.4	11.0 ± 18.3	-2.0 (-10.0 to 7.0)¶
Drowsy	20.2 ± 21.5	15.4 ± 23.2	-6.8 (-16.5 to 3.5)¶

\* Data are presented as means ± SD. Data from the secondary outcomes not presented here are shown in the Appendix Table (available at [www.annals.org](http://www.annals.org)). LDL = low-density lipoprotein; NHP = Nottingham Health Profile; SF-36 = Short Form-36 Health Survey; SHBG = sex hormone-binding globulin; TSH = thyroid-stimulating hormone.

† L-thyroxine, 100  $\mu\text{g/d}$ .

‡ L-thyroxine, 75  $\mu\text{g/d}$ , plus liothyronine, 5  $\mu\text{g/d}$ .

§ Adjusted for subject and period effects.

|| Urinary collagen degradation products were measured in 19 patients.

¶ Differences are Hodges-Lehman estimates of median differences between groups.

**Table 2. Primary and Selected Secondary Outcomes in the 26 Hypothyroid Patients Who Completed the Crossover Study: Data from Add-On Combination Treatment\***

Outcome	Standard Treatment†	Add-On Combination Treatment‡	Difference (95% CI)
<b>Biochemical variables</b>			
TSH level, <i>mU/L</i>	1.95 ± 1.44	1.09 ± 1.33	-0.85 (-1.43 to -0.27)
Free thyroxine level, <i>pmol/L</i>	20.7 ± 3.4	17.3 ± 3.7	-3.4 (-5.0 to -1.9)
Free triiodothyronine level, <i>pmol/L</i>	5.1 ± 1.5	5.9 ± 1.8	0.8 (0.1 to 1.5)
SHBG level, <i>nmol/L</i>	35.9 ± 24.0	39.5 ± 22.1	3.6 (-4.2 to 11.5)
Total cholesterol level			
In <i>mmol/L</i>	5.2 ± 1.0	5.1 ± 1.1	-0.1 (-0.3 to 0.2)
In <i>mg/dL</i>	201 ± 39	197 ± 43	-4 (-12 to 8)
LDL cholesterol level			
In <i>mmol/L</i>	3.0 ± 1.0	3.0 ± 1.0	-0.05 (-0.30 to 0.20)
In <i>mg/dL</i>	116 ± 39	116 ± 39	-2 (-12 to 8)
Ratio of urinary deoxyipyridolines to creatinine, $\mu\text{mol/S}$	9.4 ± 3.4	12.2 ± 4.1	2.8 (1.5 to 4.0)
<b>Clinical variables</b>			
Ankle reflex relaxation time, <i>ms</i>	0.18 ± 0.02	0.17 ± 0.01	-0.01 (-0.02 to 0.00)
Zulewski score	0.5 ± 0.6	0.1 ± 0.5	-1.0 (-1.5 to -0.1)
Body temperature, °C	36.4 ± 0.2	36.6 ± 0.2	0.2 (0.1 to 0.3)
<b>Profile of Mood States scores</b>			
Tension-anxiety	11.1 ± 6.5	12.8 ± 8.2	1.7 (-1.2 to 4.6)
Depression-dejection	7.8 ± 7.4	8.5 ± 7.8	0.7 (-2.1 to 3.6)
Anger-hostility	9.5 ± 7.3	11.1 ± 7.4	1.6 (-1.5 to 4.7)
Vigor-activity	16.3 ± 4.4	17.0 ± 6.0	0.7 (-1.8 to 3.2)
Fatigue-inertia	6.7 ± 5.4	7.3 ± 5.0	0.6 (-1.1 to 2.4)
Confusion-bewilderment	7.5 ± 4.9	8.5 ± 6.0	1.0 (-0.7 to 2.6)
<b>Cognitive performance scores</b>			
Digit Symbol Substitution Test			
Pairs	45.9 ± 21.4	48.4 ± 21.1	2.5 (-0.2 to 5.3)
Copies	81.5 ± 20.5	83.8 ± 17.2	8.5 (3.0 to 14.0)
Difference	35.7 ± 15.8	35.3 ± 15.1	-0.4 (-3.7 to 2.9)
Digit Span Test			
Forward	7.1 ± 3.0	7.5 ± 2.6	0.4 (-0.1 to 0.9)
Backward	5.3 ± 2.6	5.7 ± 3.0	0.4 (-0.4 to 1.2)
Total	12.4 ± 5.3	13.1 ± 5.3	0.7 (-0.3 to 1.7)
Visual Scanning Test			
Time	109.3 ± 46.6	99.3 ± 46.4	-10.0 (-26.0 to -0.9)
Items found	58.5 ± 2.1	58.7 ± 1.5	0.0 (-1.0 to 1.5)
Errors	0.0 ± 0.0	0.0 ± 0.0	0.0 (0.0 to 0.0)
<b>Quality-of-life scores</b>			
SF-36-general health NHP			
Total	60.9 ± 17.1	61.8 ± 17.3	0.9 (-5.0 to 6.9)
Emotional	8.8 ± 6.8	8.7 ± 6.5	0.0 (-1.3 to 1.2)
Energy	13.1 ± 10.8	13.5 ± 12.2	0.0 (-2.4 to 7.2)
Social	3.8 ± 6.7	3.8 ± 6.1	0.0 (-7.0 to 7.0)
Social	4.8 ± 10.3	6.4 ± 9.8	0.0 (-0.1 to 13.9)
<b>Visual Analogue Mental Scale scores</b>			
Depressed	23.8 ± 28.8	17.0 ± 20.1	-6.8 (-17.0 to 3.5)
Blurred vision	25.2 ± 29.1	24.1 ± 28.2	1.5 (-6.5 to 7.0)
Nauseated	12.5 ± 21.4	15.8 ± 24.0	2.5 (-3.0 to 9.0)
Drowsy	20.2 ± 21.5	19.7 ± 26.7	-1.8 (-14.0 to 9.5)

\* Data are presented as means ± SD. Data from the secondary outcomes not presented here are shown in the Appendix Table (available at [www.annals.org](http://www.annals.org)). LDL = low-density lipoprotein; NHP = Nottingham Health Profile; SF-36 = Short Form-36 Health Survey; SHBG = sex hormone-binding globulin; TSH = thyroid-stimulating hormone.

† L-thyroxine, 100  $\mu\text{g/d}$ .

‡ L-thyroxine, 87.5  $\mu\text{g/d}$ , plus liothyronine, 7.5  $\mu\text{g/d}$ .

§ Urinary collagen degradation products were measured in 19 patients.

|| Differences are Hodges-Lehman estimates of median differences between groups.

in serum thyroid hormone concentrations similar to those of controls, with the exception of increased free thyroxine levels, whereas levels of TSH, free thyroxine, and free triiodothyronine did not differ from those of controls after

combination treatment. On the contrary, serum TSH levels were decreased compared with controls after the add-on combination regimen, further suggesting overtreatment with this combination. No statistically significant differ-

**Table 3. Primary and Selected Secondary Outcomes in the Control Group of 20 Euthyroid Healthy Women\***

Outcome	Value
<b>Biochemical variables</b>	
TSH level, mU/L	1.91 ± 0.90†
Free thyroxine level, pmol/L	16.9 ± 1.8‡
Free triiodothyronine level, pmol/L	5.1 ± 1.3
SHBG level, nmol/L	29 ± 24
Total cholesterol level, mmol/L (mg/dL)	5.2 ± 1.1 (201 ± 43)
LDL cholesterol level, mmol/L (mg/dL)	3.2 ± 0.8 (124 ± 31)
Ratio of urinary deoxypyridolines to creatinine, μmol/§	9.0 ± 2.6†
<b>Clinical variables</b>	
Ankle reflex relaxation time, ms	0.17 ± 0.02
Zulewski score	0.4 ± 0.8
Body temperature, °C	36.5 ± 0.2†
<b>Profile of Mood States scores</b>	
Tension–anxiety	8.9 ± 4.4
Depression–dejection	5.4 ± 7.4
Anger–hostility	9.3 ± 5.0
Vigor–activity	19.7 ± 5.2
Fatigue–inertia	5.9 ± 4.1
Confusion–bewilderment	6.4 ± 4.1
<b>Cognitive performance scores</b>	
Digit Symbol Substitution Test	
Pairs	48.6 ± 15.2
Copies	85.9 ± 13.4
Difference	37.3 ± 10.8
Digit Span Test	
Forward	8.5 ± 2.1
Backward	6.6 ± 2.0
Total	15.1 ± 3.9
Visual Scanning Test	
Time	81.6 ± 27.7‡
Items found	58.1 ± 2.3
Errors	0.0 ± 0.0
<b>Quality-of-life scores</b>	
SF-36–general health NHP	
Total	3.0 ± 3.2†
Emotional	4.1 ± 4.7†
Energy	0.0 ± 0.0†
Social	0.0 ± 0.0†
<b>Visual Analogue Mental Scale scores</b>	
Depressed	5.5 ± 10.2†
Blurred vision	3.1 ± 6.0†
Nauseated	1.9 ± 3.2†
Drowsy	3.7 ± 7.7†

\* Data are presented as means ± SD. Data from the secondary outcomes not presented here are shown in the Appendix Table (available at [www.annals.org](http://www.annals.org)). LDL = low-density lipoprotein; NHP = Nottingham Health Profile; SF-36 = Short Form-36 Health Survey; SHBG = sex hormone-binding globulin; TSH = thyroid-stimulating hormone.

†  $P \leq 0.05$  when compared with L-thyroxine, 87.5 μg/d, + liothyronine, 7.5 μg/d.

‡  $P \leq 0.05$  when compared with L-thyroxine, 100 μg/d.

§ Urinary collagen degradation products were measured in 12 controls.

||  $P \leq 0.05$  when compared with L-thyroxine, 75 μg/d, + liothyronine, 5 μg/d.

ences between controls and patients were observed in any scale of the POMS, the Digit Symbol Substitution Test, and the Digit Span Test, regardless of the treatment applied. Patients performed worse than controls in the time score of the Visual Scanning Test after standard and com-

ination treatment, but not after add-on combination treatment.

Of note, when compared with euthyroid controls, patients presented with worse scores on the general health item of Short Form-36 Health Survey; on the total, emotional, energy, and social scores of the Nottingham Health Profile; and on the depression, nausea, blurred vision, and drowsiness VAMS, regardless of the treatment applied. Also compared with euthyroid controls, the isovolumic relaxation time and some brainstem auditory evoked potentials were worse in patients after standard and combination treatment, but not after add-on combination treatment. Nevertheless, all of the individual values for these evoked potentials were within the normal ranges. No other differences were observed between patients and controls in any other primary or secondary outcomes.

### Sequence and Period Effects

Statistically significant sequence effects were found for free triiodothyronine levels, low-density lipoprotein cholesterol levels, and body temperature. We explored this by adjusting these results by baseline values and reanalyzing the data. No statistically significant sequence effect persisted once we adjusted for baseline differences, so we concluded that carryover effects were unlikely. However, for completeness, we present results for these outcomes both overall and by sequence (Table 1). Of all of the variables studied here, an unexplained yet statistically significant period effect was found only for right P-100 amplitude in visual evoked potentials.

### Adverse Effects

No adverse effects were reported with any of the treatments. Moreover, the proportion of increased heart rate readings (>120 beats/min in daytime or >100 beats/min at nighttime) in the patients who received ambulatory monitoring was similar (chi-square value, 1.95;  $P > 0.2$ ) after standard treatment (13 of 420 readings), after combination treatment (13 of 376 readings), and after add-on combination treatment (7 of 377 readings).

## DISCUSSION

### Interpretation

According to our present results, treatment of primary hypothyroidism with L-thyroxine–liothyronine combinations matching the proportions present in human thyroid secretions does not offer clear advantages over standard treatment with L-thyroxine alone. None of the quality-of-life and mood indexes studied improved with L-thyroxine–liothyronine combinations compared with standard treatment. In a previous study, we compared the same quality-of-life and mood indexes in patients with differentiated thyroid cancer in 2 instances, the first while they were experiencing mild or subclinical hyperthyroidism due to TSH-suppressive therapy and the second several days after withdrawal of L-thyroxine, when serum levels of free thy-

roxine and free triiodothyronine were within the normal range (27). We found very few changes in quality of life or mood despite more marked changes in thyroid hormone levels than those observed in the present study, suggesting that these indexes are relatively insensitive to thyroid hormones. Moreover, the rat cerebral cortex has an excellent homeostasis in triiodothyronine concentrations when thyroxine alone is infused (4), but this homeostasis is lost when triiodothyronine alone is infused (32). Therefore, it is unlikely that supplementation of L-thyroxine with liothyronine in humans improves indexes dependent on an organ that is itself virtually independent of the changes in circulating thyroid hormones when L-thyroxine alone is used for replacement therapy. However, it is perplexing that despite the lack of objective advantages, most patients preferred combined treatment. It is possible that combined L-thyroxine–liothyronine treatment offers subtle improvements in well-being that may not be detected by the relatively insensitive methods used here to study quality of life.

Combinations of L-thyroxine and liothyronine did not clearly improve biological thyroid hormone end points pertaining to other organs and systems. We observed a slight improvement in the Digit Span Test with combination treatment compared with standard treatment, but this improvement was compensated by an undesirable increase in total and low-density lipoprotein cholesterol levels (together with the small increase in TSH levels and the small decrease in heart rate, this finding might suggest underreplacement in some organs, such as the pituitary gland, the heart, and the liver) and in excretion of urinary deoxy-pyridolines (which, on the contrary, might suggest overreplacement in bone). Some indexes of cognitive function, brainstem auditory evoked potentials, and diastolic performance indexes were slightly better after the add-on combination treatment than after standard treatment. However, these results might be related to the fact that patients were actually overtreated with the add-on combination regimen, given that TSH levels were below the normal range in several patients and bone turnover was clearly increased. Therefore, clinicians should consider the possibility of undesirable effects when adding even small doses of liothyronine to L-thyroxine (33).

The comparison with the external euthyroid control group also provided interesting results. Perhaps the most important is that several items on the quality-of-life tests and several VAMS were worse in patients throughout the study when compared with euthyroid controls, independent of the treatment received. As previous studies showed, for hypothyroid patients receiving L-thyroxine alone (34), awareness of disease may be responsible for this difference (35, 36).

The finding that patients presented with higher serum levels of free thyroxine when receiving standard treatment than euthyroid controls who had similar TSH values is in conceptual agreement with previous results in hypothyroid humans (37) and thyroidectomized rats (4). This further

suggests that supraphysiologic thyroxine concentrations are needed to ensure euthyroidism in hypothyroid patients when L-thyroxine is used alone as replacement therapy. Our results demonstrate that this may be avoided by using L-thyroxine–liothyronine combinations, given that serum concentrations of TSH, free thyroxine, and free triiodothyronine in patients receiving combination treatment were not different compared with controls. However, combination treatment did not offer other substantial advantages over treatment with L-thyroxine alone.

### Generalizability

Because we included patients with overt primary hypothyroidism, in whom residual thyroid secretion is unlikely, our results may be extrapolated to most hypothyroid patients provided that thyroid hormone is given for replacement therapy, not with the aim of suppressing endogenous TSH secretion. This is important because the improvement in certain indexes of mood and cognitive performance with triiodothyronine substitution reported by Bunevicius and colleagues (8) was restricted to athyreotic patients with thyroid cancer who received supraphysiologic thyroid hormone doses to suppress TSH secretion; our present study did not include such patients. We administered liothyronine once daily, and although patients were evaluated during the peak postabsorption period (38) (making it unlikely that the short half-life of oral liothyronine influenced the lack of beneficial effects of L-thyroxine–liothyronine combinations), it is possible that slow-releasing forms of liothyronine might prove useful for combined L-thyroxine–liothyronine treatment in the future (39).

### Overall Evidence

Of the 6 studies to date that have evaluated L-thyroxine–liothyronine treatment for hypothyroidism (Table 4), only the study by Bunevicius and colleagues (7, 8) found advantages of combined treatment over treatment with L-thyroxine alone. However, these beneficial effects appeared to be restricted to athyreotic patients with thyroid cancer who received TSH-suppressive treatment.

Our present study not only confirms the lack of benefits of L-thyroxine–liothyronine combinations but almost definitely solves some questions that had not been addressed in previous studies (36). First, instead of substituting liothyronine for part of the L-thyroxine dose, we used 2 fixed combinations of L-thyroxine–liothyronine, in proportions based on normal human thyroid secretion. In most studies, with the exception of that by Siegmund and associates (33), the amount of liothyronine used was variable and excessive compared with that of L-thyroxine. Second, to avoid patient heterogeneity, we included only women who had been treated with the same L-thyroxine dose for at least 1 year before entering the study, allowing us to ensure that all patients received exactly the same doses of L-thyroxine and liothyronine at each period of treatment. Third, because patients with subclinical hypothy-

Table 4. Summary of Studies Evaluating L-Thyroxine–Liothyronine Combinations for the Treatment of Hypothyroidism\*

Variable	Smith et al. (6)	Bunevicius et al. (7, 8)	Walsh et al. (9)	Sawka et al. (11)	Clyde et al. (10)	Siegmund et al. (33)	Present Study
Treatment approach	Tablets of L-thyroxine, 80 $\mu$ g, + liothyronine, 20 $\mu$ g, vs. tablets of L-thyroxine, 100 $\mu$ g <sup>†</sup>	T <sub>3</sub> substitution	T <sub>3</sub> substitution	T <sub>3</sub> substitution	T <sub>3</sub> substitution	Physiologic proportion of L-thyroxine–liothyronine	Physiologic proportion of L-thyroxine–liothyronine
L-thyroxine–liothyronine doses	Variable	Variable	Variable	Variable	Variable	Variable	Fixed
Design	Crossover	Crossover	Crossover	Parallel	Parallel	Crossover	Crossover
Degree of hypothyroidism	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Overt hypothyroidism
Prestudy period with stable L-thyroxine dose, mo	≥6	≥3	≥2	≥6	≥3	Not specified	≥12
Treatment periods, wk	8	5	10	12–15	16	12	8
Patients analyzed, n	87	33, 26	101	39	44	23	26
Sample size analysis	No	No	Yes	No	Yes	Yes <sup>‡</sup>	Yes
Outcomes <sup>§</sup>	Thyroid function, patients' preference	Thyroid function, quality of life, mood tests, psychometric performance, patients' preference  Few biological end points	Thyroid function, quality of life, mood tests, psychometric performance, patients' preference  Few biological end points	Thyroid function, quality of life, mood tests, psychometric performance	Thyroid function, quality of life, mood tests, psychometric performance  Few biological end points	Thyroid function, quality of life, mood tests, psychometric performance, pharmacokinetics	Thyroid function, quality of life, mood tests, psychometric performance, patients' preference  Multiple biological end points
External euthyroid control group	No	No	No	No	No	No	Yes
Benefits of L-thyroxine + liothyronine	No	Yes	No	No	No	No	No
Undesirable effects of L-thyroxine + liothyronine	Yes (symptoms of hyperthyroidism)	No	Not reported	Not reported	Not reported	Yes (serum TSH suppression and atrial arrhythmia)	Yes (serum TSH suppression and increased urinary bone-remodeling markers)
Patients' preference	L-thyroxine	L-thyroxine + liothyronine	No preference	Not assessed	Not assessed	Not assessed	L-thyroxine + liothyronine

\* A later study by Bunevicius et al. (40) was not included in this table because the small sample size of 10 patients precluded reaching a definite conclusion. T<sub>3</sub> = triiodothyronine; TSH = thyroid-stimulating hormone.

<sup>†</sup> Patients received the prestudy number of tablets (2 or 3) throughout the study.

<sup>‡</sup> A priori sample size calculation yielded a minimum of 24 patients for an 80% power when  $P < 0.05$ , but only 23 patients completed the study.

<sup>§</sup> Thyroid function tests were tests of serum thyroid hormone levels, except for the study by Smith et al. (6), in which serum protein-bound iodine levels and T<sub>3</sub>–resin uptake were measured.

roidism were excluded, all of our patients had long-term overt primary hypothyroidism, making it unlikely that residual thyroid function interfered with our results. Fourth, we did not restrict outcomes to quality of life and psychometric function but used a broad evaluation of thyroid hormone biological end points covering most organs and systems. This allowed us to detect undesirable effects of adding small doses of liothyronine to L-thyroxine, which may have been missed in all previous studies. Fifth, of importance, only our study includes an external control group of healthy euthyroid women. This allowed us to conclude that several outcomes were

affected in hypothyroid patients regardless of whether L-thyroxine or L-thyroxine–liothyronine combinations were used as replacement therapy, a potential confounding factor in previous studies.

## Conclusions

In summary, treatment with L-thyroxine–liothyronine combinations that replicate the ratio of thyroxine to triiodothyronine in human thyroid secretion does not offer any objective advantage over treatment with L-thyroxine alone, although patients prefer combination treatment. However, the addition of even minimally excessive liothy-

ronine doses to L-thyroxine may have undesirable effects. Until clear advantages of L-thyroxine–liothyronine combinations are demonstrated, L-thyroxine alone should remain the drug of choice for hypothyroid replacement therapy.

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**Appendix Table. Secondary Outcomes in the 26 Hypothyroid Patients Who Completed the Study and in the External Euthyroid Control Group of 20 Healthy Women\***

Outcome	Hypothyroid Patients							Euthyroid Controls
	Crossover Study				Add-On Period			
	L-Thyroxine, 100 µg/d	L-Thyroxine, 75 µg/d, + Liothyronine, 5 µg/d	Adjusted Difference (95% CI)†	P Value	L-Thyroxine, 87.5 µg/d, + Liothyronine, 7.5 µg/d	Difference Compared with L-Thyroxine, 100 µg/d (95% CI)	P Value	
<b>Biochemical variables</b>								
HDL cholesterol level				>0.2				>0.2
In mmol/L	1.6 ± 0.4	1.7 ± 0.5	0.0 (−0.1 to 0.1)		1.6 ± 0.4	−0.0 (−0.1 to 0.1)		1.6 ± 0.5
In mg/dL	62 ± 16	66 ± 19	0.0 (−4 to 4)		62 ± 16	0.0 (−4 to 4)		62 ± 19
Triglyceride level				>0.2				>0.2
In mmol/L	1.1 ± 0.6	1.1 ± 0.6	0.0 (−0.1 to 0.2)		1.1 ± 0.5	0.0 (−0.1 to 0.2)		0.9 ± 0.4
In mg/dL	97 ± 53	97 ± 53	0.0 (−9 to 18)		97 ± 44	0.0 (−9 to 18)		80 ± 35
AST level, U/L	20 ± 9	19 ± 6	−1 (−1 to 1)	>0.2	19 ± 7	−1 (−4 to 2)	>0.2	17 ± 3
ALT level, U/L	20 ± 11	18 ± 8	−1 (−1 to 1)	0.169	22 ± 16	2 (−5 to 8)	>0.2	16 ± 7
GGT level, U/L	41 ± 97	34 ± 51	−1 (−7 to 4)‡	>0.2	39 ± 85	−2 (−8 to 4)‡	>0.2	16 ± 5
AP level, U/L	72 ± 24	74 ± 24	2 (−3 to 6)	>0.2	71 ± 23	−1 (−6 to 4)	>0.2	79 ± 44
Serum creatinine concentration, µmol/L	72 ± 13	71 ± 11	−1 (−3 to 2)	>0.2	69 ± 9	−3 (−6 to −0.4)	0.028	73 ± 7
Ratio of urinary calcium to creatinine	0.4 ± 0.2	0.4 ± 0.2	−0.0 (−0.0 to 0.0)	>0.2	0.4 ± 0.2	0.0 (−0.1 to 0.1)	>0.2	0.4 ± 0.2
Ratio of urinary phosphate to creatinine	2.6 ± 0.6	2.7 ± 0.8	0.1 (−0.1 to 0.3)	>0.2	2.7 ± 1.2	0.2 (−0.4 to 0.7)	>0.2	2.5 ± 0.9
Ratio of urinary pyridoline to creatinine, mmol/S	2.0 ± 0.9	2.0 ± 0.7	0.0 (−0.4 to 0.4)‡	>0.2	2.6 ± 1.4	0.5 (0.1 to 1.2)‡	0.019	1.8 ± 0.4
Ratio of urinary hydroxyproline to creatinine, µmol/S	47.7 ± 15.5	53.1 ± 18.0	6.0 (−1.6 to 13.6)	0.113	57.8 ± 17.7	10.1 (2.5 to 17.7)	0.012	46.0 ± 10.1
<b>Clinical variables</b>								
BMI, kg/m <sup>2</sup>	26.9 ± 5.6	27.1 ± 5.5	0.3 (−0.1 to 0.6)	0.083	26.9 ± 5.4	0.1 (−0.3 to 0.4)	>0.2	25.4 ± 5.7
Waist-to-hip ratio	0.80 ± 0.05	0.80 ± 0.06	0.00 (−0.01 to 0.01)	>0.2	0.81 ± 0.05	0.01 (−0.00 to 0.01)	0.191	0.78 ± 0.08
Estimated fat, %	35.0 ± 8.3	35.3 ± 7.9	0.2 (−0.2 to 0.7)	>0.2	34.8 ± 8.1	−0.2 (−0.7 to 0.3)	>0.2	31.3 ± 9.1
Estimated fat, kg	24.4 ± 9.7	24.6 ± 9.3	0.3 (−0.1 to 0.7)	0.169	24.1 ± 9.4	−0.3 (−0.8 to 0.3)	>0.2	21.0 ± 9.6
<b>Quality-of-life scores</b>								
SF-36 Health Survey								
Mental health	66.9 ± 20.0	62.9 ± 20.7	−4.1 (−8.9 to 0.8)	0.096	65.7 ± 20.9	−1.2 (−7.1 to 4.7)	>0.2	74.8 ± 10.1
Physical function	83.1 ± 18.5	83.8 ± 17.7	2.5 (−5.0 to 7.5)‡	>0.2	82.9 ± 19.2	0.0 (−5.0 to 5.0)‡	>0.2	92.0 ± 10.4
Role—physical	85.6 ± 27.5	81.7 ± 32.8	0.0 (−37.5 to 25.0)‡	>0.2	77.9 ± 35.6	−25.0 (−50.0 to 12.5)‡	>0.2	93.7 ± 16.0
Role—emotional	70.5 ± 39.2	79.5 ± 35.4	16.6 (−33.6 to 66.7)‡	>0.2	79.5 ± 34.1	16.7 (−16.7 to 66.7)‡	>0.2	93.3 ± 17.4
Social function	85.6 ± 19.6	86.1 ± 21.0	6.3 (−12.5 to 18.8)‡	>0.2	85.6 ± 15.7	0.0 (−18.8 to 18.8)‡	>0.2	93.8 ± 9.5
Pain	64.8 ± 19.0	67.6 ± 21.1	2.5 (−4.2 to 9.1)	>0.2	71.9 ± 21.0	7.0 (−0.1 to 14.3)	0.055	75.1 ± 13.1
Vitality	60.8 ± 18.8	63.5 ± 19.4	2.3 (−3.0 to 7.5)	>0.2	62.9 ± 21.3	2.1 (−2.5 to 6.7)	>0.2	69.5 ± 10.2
NHP								
Sleep	7.6 ± 7.8	6.6 ± 7.0	−4.3 (−6.4 to 2.2)‡	>0.2	7.8 ± 7.7	0.0 (−4.3 to 6.5)‡	>0.2	2.8 ± 4.7
Pain	10.4 ± 15.1	9.1 ± 11.9	−3.2 (−10.3 to 6.4)‡	>0.2	8.6 ± 12.4	−6.4 (−12.8 to 6.4)‡	>0.2	3.2 ± 5.7
Mobility	11.9 ± 11.8	10.1 ± 11.6	−3.7 (−10.1 to 0.0)‡	0.167	11.9 ± 13.5	0.0 (−6.7 to 3.4)‡	>0.2	6.7 ± 9.5
<b>Visual Analogue Mental Scale scores</b>								
Sad	24.2 ± 28.8	22.3 ± 27.2	−2.1 (−11.0 to 6.9)	>0.2	20.9 ± 25.6	−3.3 (−16.6 to 9.9)	>0.2	7.8 ± 11.3
Confused	21.3 ± 27.3	18.2 ± 22.6	−3.0 (−13.3 to 7.3)	>0.2	18.6 ± 25.5	−2.8 (−12.6 to 7.1)	>0.2	9.4 ± 11.6
Fearful	11.8 ± 15.7	13.4 ± 22.0	1.3 (−4.5 to 9.5)‡	>0.2	11.3 ± 16.9	2.0 (−2.0 to 6.0)‡	>0.2	7.0 ± 12.4
Irritable	17.3 ± 17.7	21.9 ± 28.7	0.2 (−7.7 to 7.4)	>0.2	19.9 ± 23.1	2.5 (−7.3 to 12.4)	>0.2	8.9 ± 12.6
Tense	23.4 ± 24.2	27.7 ± 27.7	4.6 (−5.9 to 15.2)	>0.2	17.5 ± 18.6	−5.9 (−14.9 to 3.1)	0.189	13.1 ± 15.3
Angry	10.9 ± 13.4	17.3 ± 24.0	3.5 (−1.0 to 14.0)‡	>0.2	11.9 ± 18.4	2.0 (−5.0 to 8.0)‡	>0.2	5.4 ± 9.4
Tired	35.8 ± 30.6	34.5 ± 28.3	−0.9 (−13.7 to 12.1)	0.108	38.5 ± 31.1	2.7 (−12.3 to 17.6)	>0.2	30.6 ± 22.6
Agitated	26.0 ± 25.3	27.3 ± 31.0	1.1 (−10.9 to 12.9)	>0.2	31.6 ± 32.1	5.6 (−5.6 to 16.8)	>0.2	17.5 ± 18.7
Feel cold	18.9 ± 24.5	12.1 ± 19.7	−7.1 (−17.3 to 3.1)	>0.2	17.0 ± 22.0	−2.0 (−9.7 to 5.8)	>0.2	15.7 ± 25.8
Sleepy	17.2 ± 21.8	18.5 ± 22.8	1.2 (−7.2 to 9.6)	>0.2	18.2 ± 20.6	1.0 (−7.3 to 9.3)	>0.2	9.2 ± 13.6
Light-headed	54.7 ± 23.2	48.5 ± 24.7	−6.3 (−18.8 to 6.2)	>0.2	53.3 ± 23.3	−1.4 (−13.8 to 11.0)	>0.2	65.6 ± 27.1
Feel hot	34.8 ± 24.9	39.5 ± 35.0	4.9 (−7.2 to 16.9)	>0.2	41.7 ± 30.2	6.9 (−4.3 to 18.1)	>0.2	24.7 ± 25.7

Appendix Table—Continued

Outcome	Hypothyroid Patients							Euthyroid Controls
	Crossover Study				Add-On Period			
	L-Thyroxine, 100 $\mu\text{g}/\text{d}$	L-Thyroxine, 75 $\mu\text{g}/\text{d}$ , + Liothyronine, 5 $\mu\text{g}/\text{d}$	Adjusted Difference (95% CI) <sup>†</sup>	P Value	L-Thyroxine, 87.5 $\mu\text{g}/\text{d}$ , + Liothyronine, 7.5 $\mu\text{g}/\text{d}$	Difference Compared with L-Thyroxine, 100 $\mu\text{g}/\text{d}$ (95% CI)	P Value	
<b>Echocardiographic and other cardiovascular findings</b>								
E/A ratio	1.2 $\pm$ 0.3	1.2 $\pm$ 0.3	0.0 (−0.1 to 0.1)	>0.2	1.2 $\pm$ 0.3	0.0 (−0.1 to 0.1)	>0.2	1.4 $\pm$ 0.6
IVRT, ms	102 $\pm$ 13	105 $\pm$ 14	3 (−1 to 6)	0.098	97 $\pm$ 10	−5 (−9 to −1)	0.030	90 $\pm$ 15 <sup>¶¶</sup>
Deceleration time, ms	152 $\pm$ 29	157 $\pm$ 28	6 (−3 to 14)	0.184	157 $\pm$ 26	6 (−6 to 16)	>0.2	163 $\pm$ 27
Velocity time integral, cm	22.9 $\pm$ 3.4	22.6 $\pm$ 3.3	−0.3 (−1.0 to 0.5)	>0.2	23.1 $\pm$ 3.4	0.2 (−0.6 to 1.0)	>0.2	22.5 $\pm$ 3.2
Heart rate, beats/min	69.4 $\pm$ 8.1	66.5 $\pm$ 7.2	−3.0 (−5.7 to −0.4)	0.027	68.3 $\pm$ 8.8	−1.1 (−3.8 to 1.5)	>0.2	73.3 $\pm$ 8.4
Cardiac output, L/min	4.6 $\pm$ 0.7	4.4 $\pm$ 0.8	−0.2 (−0.4 to −0.01)	0.044	4.5 $\pm$ 0.8	−0.1 (−0.3 to 0.2)	>0.2	4.8 $\pm$ 1.1
Left atrial diameter, cm	3.2 $\pm$ 0.3	3.2 $\pm$ 0.3	0.0 (−0.1 to 0.01)	0.084	3.3 $\pm$ 0.3	0.1 (−0.1 to 0.1)	>0.2	3.1 $\pm$ 0.5
Septum thickness, cm	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1	0.0 (0.0 to 0.0) <sup>‡</sup>	>0.2	0.9 $\pm$ 0.1	0.0 (0.0 to 0.0) <sup>‡</sup>	>0.2	0.8 $\pm$ 0.1
Posterior wall thickness	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1	0.0 (0.0 to 0.0) <sup>‡</sup>	>0.2	0.9 $\pm$ 0.1	0.0 (0.0 to 0.0) <sup>‡</sup>	>0.2	0.8 $\pm$ 0.1
Shortening fraction, %	39.4 $\pm$ 3.5	38.8 $\pm$ 4.8	−0.6 (−1.8 to 0.7)	>0.2	40.3 $\pm$ 4.6	0.9 (−0.5 to 2.2)	0.189	37.9 $\pm$ 4.5
LV mass index, g/m <sup>2</sup>	78.2 $\pm$ 21.8	76.7 $\pm$ 23.3	−1.7 (−3.8 to 0.5)	0.056	77.3 $\pm$ 17.9	−0.9 (−5.8 to 4.1)	>0.2	72.4 $\pm$ 14.4
Ejection fraction	0.701 $\pm$ 0.045	0.688 $\pm$ 0.057	−0.012 (−0.028 to 0.004)	0.107	0.707 $\pm$ 0.055	0.006 (−0.010 to 0.022)	>0.2	0.679 $\pm$ 0.057
Systolic blood pressure, mm Hg	120 $\pm$ 12	121 $\pm$ 10	0 (−4 to 5)	>0.2	121 $\pm$ 10	1 (−3 to 5)	>0.2	118 $\pm$ 10
Diastolic blood pressure, mm Hg	73 $\pm$ 9	73 $\pm$ 8	0 (−4 to 3)	>0.2	74 $\pm$ 9	1 (−2 to 3)	>0.2	71 $\pm$ 7
Mean blood pressure, mm Hg	86 $\pm$ 9	86 $\pm$ 7	0 (−3 to 3)	>0.2	86 $\pm$ 7	0 (−2 to 3)	>0.2	86 $\pm$ 8
SVR, dyn/s per cm <sup>−5</sup>	1887 $\pm$ 235	1993 $\pm$ 328	110 (−10 to 230)	0.070	1941 $\pm$ 284	54 (−66 to 173)	>0.2	1864 $\pm$ 391
<b>Visual evoked potentials</b>								
P-100 latency—left, ms	107 $\pm$ 10	106 $\pm$ 10	−1 (−3 to 2)	>0.2	105 $\pm$ 9	−2 (−4 to 0)	0.096	105 $\pm$ 6
P-100 latency—right, ms	107 $\pm$ 11	105 $\pm$ 10	−2 (−4 to 1)	0.195	104 $\pm$ 10	3 (−6 to 1)	0.097	105 $\pm$ 6
P-100 amplitude—left, $\mu\text{V}$	6.6 $\pm$ 3.4	6.3 $\pm$ 3.9	−0.4 (−1.5 to 0.6)	>0.2	7.0 $\pm$ 3.3	0.4 (−0.8 to 1.6)	>0.2	7.0 $\pm$ 3.1
P-100 amplitude—right, $\mu\text{V}$	6.3 $\pm$ 2.8	5.8 $\pm$ 3.5	−0.6 (−1.6 to 0.4)	>0.2	6.8 $\pm$ 3.0	0.5 (−0.3 to 1.3)	0.192	6.8 $\pm$ 2.6
<b>Brainstem auditory evoked potentials</b>								
I latency—left, ms	1.75 $\pm$ 0.14	1.73 $\pm$ 0.14	−0.02 (−0.06 to 0.02)	>0.2	1.74 $\pm$ 0.12	−0.01 (−0.05 to 0.04)	>0.2	1.69 $\pm$ 0.13
I latency—right, ms	1.76 $\pm$ 0.11	1.72 $\pm$ 0.12	−0.04 (−0.09 to 0.01)	0.087	1.74 $\pm$ 0.11	−0.02 (−0.07 to 0.03)	>0.2	1.66 $\pm$ 0.11 <sup>¶¶</sup>
III latency—left, ms	3.86 $\pm$ 0.15	3.88 $\pm$ 0.24	0.01 (−0.06 to 0.09)	>0.2	3.82 $\pm$ 0.14	−0.05 (−0.08 to −0.01)	0.014	3.79 $\pm$ 0.22
III latency—right, ms	3.83 $\pm$ 0.15	3.83 $\pm$ 0.16	0.00 (−0.04 to 0.04)	>0.2	3.82 $\pm$ 0.15	−0.01 (−0.05 to 0.03)	>0.2	3.73 $\pm$ 0.15
V latency—left, ms	5.88 $\pm$ 0.28	5.89 $\pm$ 0.35	0.01 (−0.05 to 0.07)	>0.2	5.83 $\pm$ 0.23	−0.05 (−0.10 to 0.00)	0.066	5.70 $\pm$ 0.25 <sup>¶¶</sup>
V latency—right, ms	5.84 $\pm$ 0.19	5.83 $\pm$ 0.19	−0.01 (−0.05 to 0.03)	>0.2	5.82 $\pm$ 0.16	−0.02 (−0.06 to 0.01)	>0.2	5.68 $\pm$ 0.17 <sup>¶¶</sup>
I–V interlatency—left, ms	4.13 $\pm$ 0.22	4.16 $\pm$ 0.24	0.03 (−0.03 to 0.08)	>0.2	4.08 $\pm$ 0.16	−0.05 (−0.10 to 0.01)	0.075	4.01 $\pm$ 0.16 <sup>¶¶</sup>
I–V interlatency—right, ms	4.09 $\pm$ 0.18	4.09 $\pm$ 0.16	0.01 (−0.05 to 0.06)	>0.2	4.08 $\pm$ 0.13	−0.01 (−0.06 to 0.04)	>0.2	4.07 $\pm$ 0.67

\* Data are presented as means  $\pm$  SD. ALT = alanine aminotransferase; AP = total alkaline phosphatase; AST = aspartate aminotransferase; BMI = body mass index; E/A ratio = ratio of mitral valve flow velocity curve at the early phase to mitral valve flow velocity curve at the maximal late flow; GGT =  $\gamma$ -glutamyltransferase; HDL = high-density lipoprotein; IVRT = isovolumic relaxation time; LV = left ventricle; NHP = Nottingham Health Profile; SVR = systemic vascular resistance.

<sup>†</sup> Adjusted for subject and period and effects.

<sup>‡</sup> Differences are Hodges-Lehman estimates of median differences between groups.

<sup>§</sup> Urinary collagen degradation products were measured in 19 patients and 12 controls.

<sup>¶</sup>  $P \leq 0.05$  when compared with L-thyroxine, 100  $\mu\text{g}/\text{d}$ .

<sup>¶¶</sup>  $P \leq 0.05$  when compared with L-thyroxine, 75  $\mu\text{g}/\text{d}$ , + liothyronine, 5  $\mu\text{g}/\text{d}$ .

\*\*  $P \leq 0.05$  when compared with L-thyroxine, 87.5  $\mu\text{g}/\text{d}$ , + liothyronine, 7.5  $\mu\text{g}/\text{d}$ .